REMARKS

The foregoing amendments are presented to place the application in compliance with the sequence rules under 37 CFR 1.821-1.825.

Applicants have submitted a Sequence Listing in both paper and computer readable form as required by 37 C.F.R. 1.821(c) and (e). Amendments directing its entry into the specification have also been incorporated herein. The content of the paper and computer readable copies are the same and no new matter has been added.

A copy of the Notice is also attached as required.

Also, the nucleotide sequences disclosed in the specification which represent SEQ ID Nos: 7-10 have been identified and labeled in accordance with U. S. practice.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

In view of the foregoing, it is believed that each requirement set forth in the Notice has been satisfied, and that the application is now in compliance with the sequence rules under 37 CFR 1.821-1.825. Accordingly, favorable examination on the merits is respectfully requested.

Respectfully submitted,

Osamu NISHIMURA et al.

By: _____

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May 1, 2003

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,871	05/07/2001	Osamu Nishimura	2001_0291A	6427

513 7590 04/01/2003

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WASHINGTON, DC 20006-1021

EXAMINER
LUKTON, DAVID

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/806871			

EXAMINER	
ART UNIT	PAPER NUMBER
	9

DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Please see the attached communication regarding sequence listings.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

See, for example, the sequences on page 39

Applicant is given ONE MONTH from the mailing date of this communication within which to comply with the sequence rules, 37 CFR 1.821 - 1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

*

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600

09/806 871

Application No.:

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [x] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- [x] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [x] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked –up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other:

Applicant Must Provide:

- [x] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [x] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [x] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g).

For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (703) 308-4216 or (703) 308-2923
- For CRF Submission Help, call (703) 308-4212
- For PatentIn software Program Support:
  - HELP DESK: (703) 739-8559, ext 508, M-F, 8 AM to 5 PM EST except holidays
  - Email: PATIN21HELP@uspto.gov
  - To purchase PatentIn sofftware: (703) 306-2600

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE

Gly	8.0	8
Ala	6.2	6
Cys[2)]	N.D.	4
Val	7.0	7
Met	2.9	3
Ile	6.5	7
Leu	24.3	25
Tyr	5.9	6
Phe	12.2	12
His	3.1	3
Lys	7.1	7
Arg	10.7	11
Trp	N.D.	1

Acid hydrolysis (mean value of 24-hours and 48-hour hydrolysis, at 110°C, with 6N HCl-1% phenol). Analysis was performed using approximately 20 μg.

1) Value extrapolated at 0 hours.

2) Not detected.

Example 14 (Measurement of 20K-hGH activity)

The growth promoting activity of the 20K-hGH obtained in Example 12 on Nb2 cells [Journal of Clinical Endocrinology and Metabolism, Vol. 51, p. 1058 (1980)] was confirmed.

Example 15 (Manufacture of human BTC which possesses methionine residue (human Met-BTC))

In accordance with Examples 4 through 6, 8, and 13 of Unexamined Kokai Application Heisei 6-87894 (EP-A-0555785), human Met-BTC was manufactured in the following method.

(Construction of human BTC cDNA expression plasmid in *E. coli*)

The 0.6 Kb EcoRI-BamHI fragment, which codes for

human pro-BTC (1-147 amino acid residue), was isolated from Plasmid pTB1515 described in Example 5 of Unexamined Kokai Application Heisei 6-87894 (EP-A-0555785). Upon ligating a synthetic adapter with ATG translation initiation codon (5'-TATGGATGGG-3' (SEQ ID NO: 7); 5'-AATTCCCATCCA-3' (SEQ ID NO: 8)) into the EcoRI site of the 0.6 Kb fragment, the 0.6 Kb NdeI-BamHI fragment generated was inserted into plasmid pET-3c containing a T7 promoter (Gene, Vol. 56, p. 125 (1987)), to construct plasmid pTB1505.

In order to obtain DNA fragments that code for the 80 amino acid residues in human BTC (1 (Asp) through 80 (Tyr) in Figures 10-1 and 10-2 (Unexamined Kokai Application Heisei 6-87894 (EP-A-0555785)), PCR (polymerase chain reaction) was performed using plasmid pTB1505 as the template and two oligonucleotides (5'-ATACATATGGATGGGAATTCCA-3' (SEQ ID NO: 9); 5'-CCGGATCCTAGTAAAACAAGTCAACTCT-3' (SEQ ID NO: 10)) as the primer. The product was digested with NdeI and BamHI, followed by fractionation via electrophoresis with 2.0% agarose gel, to isolate the targetted 0.25 Kb DNA fragment. This 0.25 Kb NdeI-BamHI fragment was ligated to the downstream of the T7 promoter of pET-3c using T4DNA ligase, to obtain plasmid pTB1516 (See Figure 13 of Unexamined Kokai Application Heisei 6-87894 (EP-A-0555785)).

(Expression of human Met-BTC in *E. coli*)

E. coli MM294 was lysogenized by a recombinant lambda-phage containing the T7 RNA polymerase gene (Studier, supra). Subsequently, plasmid pLysS was introduced into this *E. coli* MM294(DE3), to obtain *E. coli* MM294(DE3)/pLysS. The plasmid pTB1516 obtained in the aforementioned Reference was introduced into these cells, to obtain *E. coli* MM294(DE3)/pLysS, pTB1516.

This transformant was cultured with shaking for 8